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Credit Author Statement:

Luciana Maria Gulisano: writing, original draft preparation, investigation, editing, conceptualization, methodology.

Joaquín Ianiro Swiderski: writing and investigation.

Marisa Liliana Fernandez: reviewing, investigation, supervision

Juan Franco Giuliano: supervision

Ana Laura Fernandez Stepa: writing

Cecilia Dominguez: writing

Nicolás Nahoum: writing

Johana Jourdan: writing

José Luis Trombetta: supervision

Julián Luis García: writing and supervision

Acute colonic pseudo-obstruction syndrome in patients with severe COVID-19 in Buenos Aires, Argentina

Luciana María Gulisano [a], Joaquín José Ianiro Swiderski [a], Marisa Liliana Fernández [a], Juan Franco Giuliano [b], Ana Laura Fernández Stepa [a], Cecilia Dominguez[c], Nicolás Nahoum [a], Johana Jourdan [a], Luis Ángel Trombetta[a], Julián Luis García [a]

[a] *Hospital de Infecciosas F.J. Muñiz, Department of Infectious Diseases, Buenos Aires, Argentina*
[b] *Hospital de Infecciosas F.J. Muñiz, Unit of Surgery, Buenos Aires, Argentina*
[c] *Hospital de Infecciosas F.J. Muñiz, Intensive Care Unit, Buenos Aires, Argentina*

Abstract

Background: Several gastrointestinal complications have been reported in patients with COVID-19, including motility disorders, such as acute colonic pseudo-obstruction (ACPO). This affection is characterized by colonic distention in the absence of mechanical obstruction. ACPO in the context of severe COVID-19 may be related to neurotropism and direct damage of SARS-CoV-2 in enterocytes.

Method: We conducted a retrospective study of patients who were hospitalized for critical COVID-19 and developed ACPO between March 2020 and September 2021. The diagnostic criteria to define ACPO was the presence of 2 or more of the following: abdominal distension, abdominal pain, and changes in the bowel movements, associated with distension of the colon in computed tomography. Data of sex, age, past medical history, treatment, and outcomes were collected.

Results: Five patients were detected. All required admission to the Intensive Care Unit. The ACPO syndrome developed with a mean of 33.8 days from the onset of symptoms. The mean duration of the ACPO syndrome was 24.6 days. The treatment included colonic decompression with placement of rectal and nasogastric tubes, endoscopy decompression in two patients, bowel rest, fluid, and electrolytes replacement. One patient died. The remaining resolved the gastrointestinal symptoms without surgery.

Conclusions: ACPO is an infrequent complication in patients with COVID-19. It occurs especially in patients with critical condition, who require prolonged stays in intensive care and multiple pharmacological treatments. It is important to recognize its presence early and thus establish an appropriate treatment, since the risk of complications is high.

Keywords: SARS-CoV-2, paralytic ileus, Ogilvie's syndrome, coronavirus, acute colonic pseudo-obstruction syndrome, ACPO

1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) reported its first confirmed case in December 2019 in Wuhan, China. Since then, it has caused a pandemic that as of June 2022 has more than 539 million confirmed cases and more than 6 million deaths [1].

SARS-CoV-2 mainly affects the respiratory system, progressing to severe forms in 10 to 20% of patients [2]. Uncommonly, it can produce gastrointestinal, dermatological, neurological, cardiovascular, and hepatic manifestations, among others. These manifestations can present with variable clinical features, and they could be life-threatening [3-4].

Gastrointestinal symptoms have a prevalence of 17.6% in severe disease and 11.8% in mild to moderate forms and may be the initial or even the only manifestations of the disease [5]. The most frequent digestive symptoms are diarrhea (12.5%), nausea and/or vomiting (10.2%) and abdominal pain (9.2%). Gastrointestinal complications such as hepatitis, cholecystitis, pancreatitis, ischemia, gastrointestinal perforation, bleeding and hypomotility, including acute colonic pseudo-obstruction (ACPO) have also been described in patients with critical COVID-19 [6-10].

This study describes the clinical, laboratory and imaging aspects of 5 patients who were hospitalized with a diagnosis of critical pneumonia due to COVID-19 and developed colonic pseudo-obstruction syndrome.

2. Materials and Methods

We conducted a retrospective study of patients who were hospitalized at the F. J. Muñiz Infectious Diseases Hospital (Buenos Aires, Argentina) for COVID-19 associated with ACPO between March 2020 and September 2021.

Clinical records were reviewed. It was collected data on age, sex, comorbidities, serological diagnosis of Chagas disease, date of onset of symptoms, need for intensive care unit (ICU), mechanical ventilation (MV), laboratory results, *Clostridioides difficile* antigen and toxin, and computed tomography (CT) scan. Medical data related to treatment and hospitalization complications were also collected e.g., hospital-acquired infections such as ventilator-associated pneumonia (VAP), bacteremia and hydro-electrolytic disorders.

The diagnosis of SARS-CoV-2 was made in all cases by PCR in nasopharyngeal swabs. The diagnostic criteria to define ACPO syndrome were the presence of 2 or more of the following issues: abdominal distension, abdominal pain, and changes in the bowel movements (e.g., constipation and/or diarrhea), associated with presence of colonic and/or bowel loops distention in CT scan. In all cases, intra or extraluminal mechanical obstruction was discarded.

Categorical variables were presented as absolute numbers and proportions, and continuous variables were expressed as means and ranges. Results were analyzed using Microsoft Excel (version 2108) on Windows 10 Professional (version 21H1).

This study was evaluated and approved by the F.J. Muñiz Infectious Diseases Hospital independent ethics committee. Informed consent was exempted according to national and international regulations.

3. Results

Five patients with critical COVID-19 and ACPO syndrome were detected. Four were men, with a mean age of 58 years old (range 51-66). Clinical and epidemiological characteristics are detailed in Table 1.

All cases presented with diarrhea at the beginning of their COVID-19 and required admission to the Intensive Care Unit (ICU) with mechanical ventilation (MV). The mean duration of hospitalization was 69 days (range 15-144). The average stay in ICU was 33.6 days (range 11-56) and the MV requirement was 10-53 days (mean 25.8 days). Two patients required tracheotomy, one for 24 days and the other one for 53 days.

The ACPO syndrome developed in a mean of 33.8 days from the onset of COVID-19 symptoms (range 22-52). Four of the five patients developed the colonic pseudo-obstruction symptoms once they improve their respiratory status. The five patients had diarrhea, abdominal pain and marked abdominal distention. Three patients presented vomiting, one of them had fecaloid vomit. CT scan showed colonic distention in all cases, and one patient also developed terminal ileum distention. (Figure 1)

Among the long hospitalization stay, all the patients of this study had healthcare-associated infections. All of them had one or more events of ventilator-associated pneumonia (VAP) and 4 had at least one episode of gram-negative bacteremia at the same time as ACPO syndrome. The bloodstream bacterial isolates were *Klebsiella pneumoniae*, *Proteus mirabilis, Pseudomonas aeruginosa*, and *Enterococcus faecalis*. All of them had negative *C. difficile* antigen and toxin.

The laboratories findings showed liver enzymes elevation in 4 patients. All patients had hypoalbuminemia and elevated acute-phase reactants such as ferritin, D dimer, Protein C reactive (CRP), erythrocyte sedimentation rate (ESR) (Table 2). The 5 patients of this series presented moderate to severe hypokalemia (nadir mean 2.32 mmol/l, range 1.9 - 2.7), requiring daily replacement of potassium for a mean of 41.4 days (range 13-74). No stool PCR SARS-CoV-2 was tested.

Other major concomitant medical complications found in this series were culture-negative neutrocytic ascites, acute pancreatitis, and thrombotic events on two patients, one coronary thrombosis and the other axillary and subclavian vein thrombosis.

The therapeutic applied was bowel rest with placement of rectal and nasogastric tubes, fluid and electrolytes replacement with potassium chloride and intravenous magnesium sulfate in all cases. One patient received neostigmine, another rifaximin and a third both medications. Two patients received oral vancomycin and metronidazole treatments. Endoscopy was performed on two patients for diagnostic and decompressive therapeutic, no macroscopy lesions were observed, and the biopsies of both patients showed normal mucous membranes.

The average duration of the pseudo-obstruction syndrome was 24.6 days (range 6-40) (Table 1). One patient died of septic shock secondary to bacteremia by carbapenemase-producing *Klebsiella pneumoniae* on day 45 of hospital admission. The remaining resolved the symptoms without surgical intervention and were discharged. (Table 1)

4. Discussion

The ACPO syndrome, also known as Ogilvie's syndrome, is a functional disorder characterized by colonic dilatation in the absence of obstructive causes. It is related to risk factors such as male sex, age over 50 years, critically ill patients, as can be seen in this case series. Among the causes associated with this syndrome are some viral infections [11], postoperative states, neurodegenerative diseases, hydro-electrolytic disorders, and drugs [12]. Its pathophysiology is not completely known; however, dysfunction of the gastrointestinal autonomic nervous system seems to be key for its development [13].

In this series we describe 5 cases with ACPO syndrome associated with severe SARS-CoV-2 infection; to the best of our knowledge, it is the largest series published to date. There are few case reports published which described this association. ACPO syndrome was clinical and radiologically diagnosed in 2 cases of 141 patients with critical COVID-19, in this cohort disorders related to intestinal hypomotility were described in almost half of the patients [6]. Another three patients who were hospitalized for critical pneumonia due to COVID-19 presented colonic ileus and coagulation disorders, one of whom required surgical intervention for intestinal ischemia [14]. Ibrahim et al. reported other two cases of SARS-CoV-2 infection that developed colonic paralytic ileus, one of which required emergency laparotomy due to perforation of the transverse colon [15]. The association between acute pancreatitis with colonic pseudo-obstruction in the context of COVID-19 have also been reported in one case report. [16]

The ACPO literature consists mainly of case reports and case series from different fields of expertise, therefore, its etiology remains difficult to address. In this study, we consider that COVID-19 could have triggered the ACPO syndrome. However, the following factors could have contributed to the ACPO development or hampered his resolution: hydro-electrolytic disorders, multiple pharmacological treatments, and the severity of the clinical status. All patients had persistent hypokalemia despite continuous parenteral potassium replacement and therefore this disorder could be interpreted secondary to the loss of water and electrolytes through a dysfunctional colonic lumen. Moreover, the fact that the patients did not show improvement after the correct electrolyte replacement allows us to infer that other pathogenic mechanisms may be involved, we could assume that hypokalemia was initially a consequence and not a cause of ACPO, but it could have been a perpetuating mechanism.

In conjunction with the reported cases, the patients of this series presented severe respiratory distress that required MV with elevated acute phase reactants. It is noteworthy that the digestive symptoms were manifested when the respiratory parameters due to COVID-19 began to improve, except for one patient. In addition, thrombotic events were diagnosed in two patients. Hypercoagulability, microangiopathy and intestinal thrombosis could contribute to development of functional alterations. In this sense, there are reports of ischemic colitis, mesenteric ischemia, and intestinal perforation in the context of SARS-CoV-2 infection [6, 15, 17-18]. We must point out that all patients required vasopressors, this fact is relevant because it could be a cause of intestinal injury due to splanchnic vasoconstriction.

In relation to other probable pathogenic mechanisms, there is evidence of the virus avidity for enteric neurons and epithelial cells of the digestive tract through the interaction of protein S with ACE2 receptors [19-21]. Xiao et al. showed the presence of inflammatory infiltrates and the viral nucleocapsid in the cytoplasm of glandular epithelial cells of the stomach, duodenum, and rectum [22]. Likewise, these receptors have been found in the enteric nervous system, with greater expression in neurons of the colon than in those of the small intestine [23-24].

Virus replication at gastrointestinal tissue can be evident as was shown the presence of RNA SARS-CoV-2 in stool samples, this finding was observed in a greater proportion in those with gastrointestinal symptoms than in those without them (54.4% vs 25.9%) [25]. The presence of viral RNA was demonstrated even when respiratory samples were negative [26]. In addition, a lower viral clearance has been reported in stool samples of convalescent patients treated with corticosteroids [27], a drug that all patients in our series received. A recent study has suggested the gastrointestinal tract as a major viral reservoir in patients with long COVID [28]. The data above can support that possible pathogenesis mechanisms of ACPO in critically ill COVID-19 patients could be directly related to the presence, replication, and persistence of the virus at the intestinal level with damage of the autonomic nervous system and decreasing gastrointestinal smooth muscle contractility. No stool PCR SARS-CoV-2 was performed in these series, as it was not used for assistance purposes. Considering the evidence published so far, we believe that running this test in patients with suspected gastrointestinal complications related with COVID-19 might be useful as a diagnosis method in the future.

Another infection to discard for dysfunction of the gastrointestinal autonomic nervous system mainly in Latin America is Chagas disease [29-30]. In Argentina, the prevalence of *Trypanosoma cruzi* infection is around 4%. All patients were tested and only one patient had reactive serologies for *T. cruzi*, evolving with resolution of the condition. Megacolon due to chronic *T. cruzi* infection is a chronic, progressive, and irreversible condition, so we can rule out its association with pseudo-obstruction in this case [31].

About ACPO syndrome treatment, support measures were used in all patients and clinical improvement was obtained by placing a rectal tube as a method of colonic decompression. Two patients received neostigmine, a parasympathomimetic that increases smooth muscle contraction. Although it has been shown to be effective in some studies, its use is associated with numerous adverse effects such as abdominal pain, bradycardia, hypotension, and bronchospasm [32-34]. As an attempt to decrease bacterial translocation, rifaximin was used in two patients. Although we do not have sufficient evidence to recommend its use, it could be considered in these cases as a modulator of possible dysbacteriosis. [35-36]

Mortality in our series was 20%, comparable to the published evidence for ACPO syndrome, which reach up to 40% in cases that require surgical intervention [37]. The patients with the highest risk of perforation are those with a cecal diameter greater than 12 cm and colonic distention longer than 6 days [38]. Although the duration of the symptoms in 4 patients of our cohort was longer than 6 days, they did not exceed the limit of 12 cm in relation to cecal diameter. No patient in our series had a bowel perforation. In the literature mortality in ACPO syndrome is related to surgical complications, but in our cohort the only death was due to an infectious complication as none needed surgery [39]. It is noteworthy that most of the patients presented one or more episodes of bacteremia due to gram-negative bacilli in the context of pseudo-obstruction. We interpreted that these episodes could be related to bacterial translocation from the intestinal lumen even in the patients with antibiotic prophylaxis.

There are some considerations to clarify, we understand that due to the retrospective characteristic of this study there could be missing data and bias, and that the number of patients is small but even that, as far as we know, it is largest series of ACPO syndrome and COVID-19 published.

5. Conclusions

The association between ACPO and COVID-19 continues to be observed randomly and scarce worldwide. As in our experience they were complexed patients that needed a long hospital stay, continue electrolytes and fluid replacement with high risk of health care associated infections we find important to communicate

the experience to increase knowledge about this entity. It is an infrequent complication that requires a high index of suspicion and adds significant morbidity and mortality. It occurs in some patients with critical COVID-19, who require prolonged stays in intensive care units and multiple pharmacological treatments. ACPO is a diagnosis of exclusion, so other etiologies must be considered. It is important that physicians recognize its presence early to establish an appropriate treatment, since the risk of complications is high.

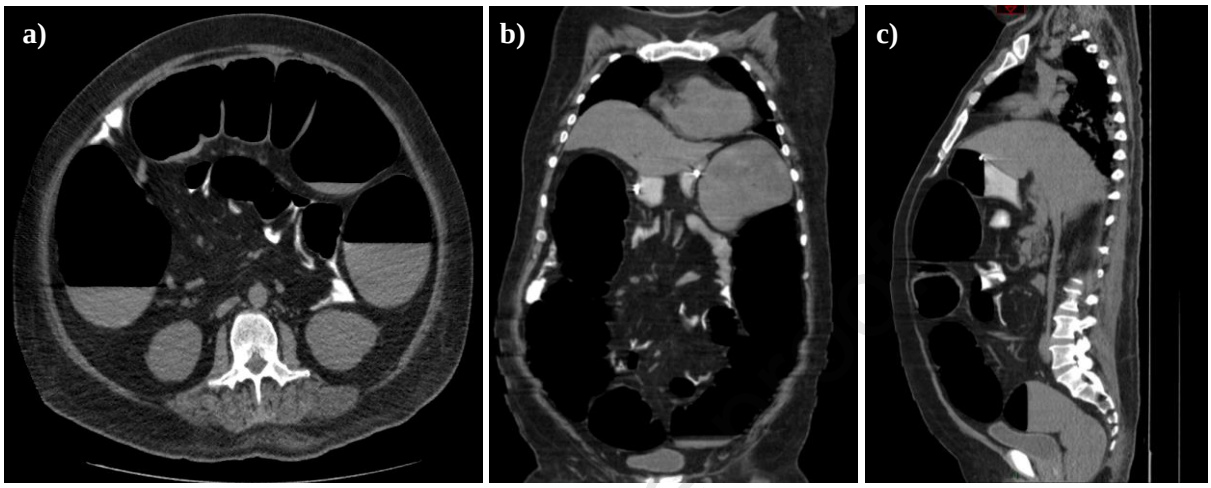

Figure 1 – Patient 3
Oral contrast-enhanced abdominal computer tomography showing generalized colonic distention with air content but with a liquid interface and thin walls: a) axial plane b) coronal plane c) sagittal plane.

Table 1
Clinical data, supplementary tests, treatment, and outcomes

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Sex	Male	Female	Male	Male	Male
Age	64 years	66 years	51 years	57 years	52 years
Nationality	Argentina	Peru	Bolivia	Bolivia	Argentina
Comorbidities	Obesity	Obesity Kidney carcinoma	Obesity Alcoholism	Obesity Alcoholism RBBB	Obesity
Chagas serology	No reactive	No reactive	No reactive	Reactive	No reactive
Early symptoms	Fever, cough, dyspnea, vomiting and diarrhea	Fever, dyspnea and diarrhea	Cough, dyspnea and diarrhea	Cough, dyspnea and diarrhea	Fever, dyspnea, cough, and diarrhea
Duration of the ileum	26 days	14 days	35 days	6 days	40 days
Abdominal CT scan	Colonic distension	Colonic and terminal ileal distention	Colonic distention	Colonic distention	Colonic distention
Cecal diameter	10.33cm	7.4cm	6.71cm	6.42cm	8.75cm
Hospital stays	45 days	15 days	103 days	43 days	144 days
Colonoscopy	Yes	No	No	No	No
Endoscopy	Yes	No	Yes	No	No
Neostigmine	Yes	No	No	Yes	No
Rifaximin	Yes	No	No	No	Yes
Corticosteroids	Yes	Yes	Yes	Yes	Yes

RBBB: Right Bundle Branch Block. CT scan: computed tomography scan.

Table 2

Laboratory findings at hospital admission

	Normal range	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
ALT	0-41 UI/l	110 U/l	24 U/L	174 U/l	81 U/l	574 U/l
AST	0-38 UI/l	91 U/l	28 U/l	401 U/l	115 U/l	964 U/l
LDH	230-460 U/l	1195 U/l	604 U/l	1151 U/l	482 U/l	1119 U/l
ESR	0-20 mm/h	29 mm	48 mm	-	4 mm	101 mm
D-Dimer	0-500 ng/ml	-	2762 ng/mL	3257 ng/mL	-	5092 ng/mL
Ferritin	30-400 ng/ml	2382 ng/mL	-	1019 ng/mL	1841 ng/mL	2173 ng/mL
CRP	0.0-5.0 mg/dL	174.3 mg/dl	-	-	96.9 ng/mL	-
Procalcitonin	0.0-0.5 ng/ml	1.90 ng/dl	0.18 ng/mL	0.47 ng/mL	0.36 ng/mL	<0.05 ng/mL
Fibrinogen	200-400 mg/dL	919 mg/mL	318 mg/mL	614 mg/mL	556 mg/mL	497 mg/dl
Albumin	3.5-5.1 g/dL	2 g/l	1.9 g/l	1.8 g/l	2.4 g/l	2.7 g/L
Amylase	28-100 U/l	69 U/l	-	92 U/l	98 U/l	161 U/l

ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, CRP: C Reactive Protein

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